IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Confirmation No.: 8347

Luis Octavio SILVA GUISASOLA, *et al.*

Serial No.: 10/542,821 Group Art Unit: 1612

Filed: July 20, 2005 Examiner: Barbara P. Badio

For: PROCESS FOR OBTAINING 17α-ACETOXY-11β-(4-N,N-DIMETHYLAMINOPHENYL)-19-NORPREGNA-4,9-DIENE-3,20-DIONE

VIA EFS-WEB
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

1. I, Antonio Lorente Bonde-Larsen, am a Spanish citizen, residing at Arribes del Duero 9, E-47151, Boecillo (Valladolid), Spain. I am the Research & Development manager of Ragactives, S.L.U. I have read and am familiar with the U.S. Patent Office Action dated November 4, 2009 concerning the subject application. I am aware that among the rejections cited in the Office Action, the Examiner rejected claims 1-8, 10, 12-14, 16-17, 19-22 and 24-26 under 35 U.S.C. 103 as purportedly being obvious over a combination of PCT WO by 96/30390 by Kim ("Kim") and PCT WO 99/45022 by Cook et al. ("Cook"). I am making this declaration to support the patentability of the claims of the above-identified application.

2. A copy of my *curriculum vitae* ("CV") is provided as attachment 2 to this declaration. My relevant educational experience is set forth under the heading "Educational Background" on p. 1 of my CV. My list of Publications is found at p. 1, whereas a list of patents/applications on which I am an inventor/co-inventor is found at p. 2. I submit that,

in accordance with the details provided in my CV, I am one having at least ordinary skill in the field of the compositions and methods recited in the claims of the present application.

3. As discussed in more detail below, the processes as claimed provide a significant purity improvement over that obtained by Kim. Before discussing the purity improvement, it is important to understand the various purification steps. In Claims 8 and 10, 17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione (VA-2914) is purified by first forming a VA-2914 isopropanol hemisolvate by dissolving VA-2914 in isopropanol under heat. The resulting solution is cooled to obtain crystalline VA-2914 isopropanol hemisolvate. The crystalline VA-2914 isopropanol hemisolvate is then isolated from the mother liquor. This isolation step separates the isopropanol hemisolvate from impurities that are soluble in isopropanol. Claim 1 depends from Claim 8, and adds the further steps of separating the VA-2914 isopropanol hemisolvate crystals and converting VA-2914 isopropanol hemisolvate into VA-2914. Claim 7 (which depends from Claim 8) specifies the manner in which the VA-2914 compound is initially obtained. The compound is initially obtained by acid hydrolysis of compound 3,3-(1,2-ethanedioxy)-5α-hydroxy-11β-(4-N,N-dimethylaminophenyl)-17α-acetoxy-19-norpregna-9-ene-20-one [carbinol acetate]. Claims 16 and 17 (which both depend from Claim 1) specify that the VA-2914 is in the form of a white crystalline solid (Claim 16), and has a melting point of around 189°C (Claim 17). Other dependent claims add further limitations to the claims, but this Declaration focuses on the process steps outlined in these claims, and how these process steps provide a product with a significantly higher purity than that obtained using the process disclosed in Kim.

4. In addition to the process claims, there are claims directed to the product itself. Claim 24 is an independent claim directed to isolated VA-2914, in the form of white crystals. Claim 25 is an independent claim directed to isolated VA-2914, in the form of crystals with a melting point of around 189°C, and Claim 26 is an independent claim directed to isolated VA-2914, in the form of white crystals with a melting point of around 189°C.

The importance of the color and melting point of the crystals is also discussed in this Declaration.

5. Kim discloses purifying raw VA-2914 by a dissolution-evaporation stage in isopropanol, followed by a dissolution-evaporation stage in ethyl acetate and a final recrystallization stage from ether (example 7, lines 26-36). That is, Kim did not isolate VA-2914 isopropanol hemisolvate from an isopropanol mother liquor (i.e., a liquid including the isopropanol solvent, any un-precipitated VA-2914 isopropanol hemisolvate, and un-precipitated impurities). Kim does not teach or suggest isolating an isopropanol solvate from a mother liquor, as claimed. Thus, any impurities that would be soluble in the mother liquor are reintroduced into the crystalline material when the isopropanol is removed by evaporation, except for impurities that are volatile enough to be removed by evaporation as the isopropanol is evaporated.

6. Kim produced VA-2914 as a yellow crystalline solid. With respect to those claims related to the isolated, purified product (i.e., Claims 24-26), Kim did not obtain isolated VA-2914 in the form of white crystals (Claim 24), isolated VA-2914 in the form of crystals with a melting point of around 189°C (Claim 25), or isolated VA-2914, in the form of white crystals with a melting point of around 189°C (Claim 26). Both melting point and color are generally accepted indications of purity, so the yellow color and lower melting point are relevant factors when considering the claimed purification process.

7. Cook discloses compounds structurally related to VA-2914. The majority of the compounds disclosed in Cook were purified by chromatography. Example 4 discloses that a compound was recrystallized from ethanol, and Example 10 discloses that a compound was recrystallized from ether/hexane. Cook does not teach that any of the compounds were first converted to an isopropanol hemisolvate and removed from a mother liquor, converting a hemisolvate to a parent compound, or recrystallizing compounds from isopropanol.

8. In the claimed processes, by forming the isopropanol hemisolvate and separating this hemisolvate from the mother liquor, impurities that are soluble in the isopropanol remain in the mother liquor and are effectively removed from the final product. Neither Kim nor Cook discloses all of the elements of the claims. Kim may or may not have formed an isopropanol hemisolvate, but such was not separated from isopropanol-soluble impurities. Cook does not disclose forming an isopropanol hemisolvate or recrystallized any products from isopropanol, so Cook would similarly never have removed isopropanol-soluble impurities from a mother liquor. However, it is precisely this process step that provides improved product purity.

9. The process of Claim 1 (which depends from Claim 8) adds the further step of desolvating the hemisolvate. As neither Kim nor Cook expressly teach or suggest forming an isopropanol hemisolvate, neither expressly teach desolvating an isopropanol hemisolvate. Again, Kim teaches purifying raw VA-2914 by a dissolution-evaporation stage in isopropanol, followed by a dissolution-evaporation stage in ethyl acetate. Even if, arguendo, Kim formed an isopropanol hemisolvate in the first dissolution-evaporation stage, and desolvated the hemisolvate in the second dissolution-evaporation stage, such was clearly not appreciated. As with Claim 8, at a minimum, Kim does not teach or suggest removing an isopropanol hemisolvate from an isopropanol mother liquor.

10. The process of Claim 7 (which depends from Claim 8) specifies the manner in which the VA-2914 compound is initially obtained. The compound is initially obtained by acid hydrolysis of compound 3,3-(1,2-ethanedioxy)-5α-hydroxy-11β-(4-N,N-dimethylaminophenyl)-17α-acetoxy-19-norpregna-9-ene-20-one [carbinol acetate]. In contrast, Kim discloses the acid hydrolysis of a compound with a hydroxy group at the 17 position a 3,3-(1,2-ethanedioxy) protecting group, and a hydroxy group at a position beta to the ethanedioxy group. The hydrolysis of the 1,2-ethanedioxy group yields a 3,3-oxo group, and the hydroxy group at the beta position is eliminated (dehydrated) to yield a double bond at the 4-position (See page 5, conversion of Compound VII to Compound VIII).

11. Kim therefore does not teach or suggest hydrolyzing the 1,2-ethanedioxy group of an intermediate including the 17α-acetoxy group. Indeed, Compound VII is prepared from Compound VI, which includes a free hydroxy group and an epoxy group, by reaction with a Grignard reagent (Kim at page 13, lines 18-22). Excess Grignard reagent (roughly 5 equivalents) is used, as the hydroxy group is converted to a magnesium alkoxide (Page 13, lines 23-30). It would not have been possible to perform Kim's purportedly improved synthesis with an acetoxy group present at the 17α-position, if such group were intended to remain on the molecule in subsequent steps (as required in pending Claim 7). The reaction product of a Grignard reagent with an ester is a tertiary alcohol. If an acetoxy group were present at the 17α-position (as in the process of claim 7), it would have been cleaved by such a great excess of Grignard reagent as employed by Kim. Accordingly, it would be impossible to modify Kim to arrive at the process of Claim 7. In contrast, the process of the invention employs a much lower excess of Grignard reagent which allows to selectively add the aryl group without affecting any of the remaining reactive groups of the molecule.

12. With respect to Claims 24-26, Kim does not teach or suggest obtaining isolated VA-2914 in the form of white crystals (Claim 24), isolated VA-2914 in the form of crystals with a melting point of around 189°C (Claim 25), or isolated VA-2914, in the form of white crystals with a melting point of around 189°C (Claim 26), and Cook does not overcome this deficiency. The melting point and color of the crystals is indicative of their relatively high purity. Kim expressly discloses forming a crystalline product with a yellow color and with a lower melting point, which makes it clear that Kim fails to teach or suggest forming VA-2914 of the same high purity as is claimed in Claims 24-26.

13. As discussed above, the claimed processes differ from the process that Kim used, in that the use of a recrystallization step from isopropanol and the removal of the crystalline material from the impurity-containing mother liquor, removes impurities that would be retained if a dissolution-evaporation step in isopropanol is used.

14. To demonstrate the unexpectedly superior purity obtainable using Applicants' claimed process over the process disclosed by Kim, a side-by-side comparison of both processes was conducted, starting from a similar raw sample of 87.5% purity. Following the process taught by Kim, the crude material (20.82 g) was dissolved in isopropanol (52 mL) and evaporated (three times) and then dissolved and evaporated in ethyl acetate (80 mL). The resulting residue was dissolved in ethyl ether (65 mL), set aside to crystallize, filtered and washed with ether (10 mL). This process afforded VA-2914 of 98.57% purity (m.p. = 183-185°C). A second sample of the same crude material (20.82 g) was subjected to the process of the invention (examples 2 and 3 of the application), leading to VA-2914 with a purity of 99.20% (white crystals, m.p. = 189°C). Purity was determined by HPLC analysis. A copy of the HPLC chromatograms of raw material (87.50% purity), VA-2914 purified by the process of Kim et al. (98.57% purity) and VA-2914 purified by the process of the invention (99.20% purity) are enclosed (Annex 1).

15. Based on an analysis of the purity of VA-2914 produced by the two processes, the data show that the claimed processes provide VA-2914 of significantly higher purity than the process disclosed by Kim et al.

16. The purity of an active pharmaceutical ingredient is not trivial, but rather, is a necessary condition for commercialization. Impurities produced during manufacturing processes must be limited to very small amounts to meet established quality standards. Indeed, purities higher than 99% are routinely requested for active pharmaceutical ingredients. As a consequence, the purity improvement achieved by the invention is essential in order to be able to commercialize VA-2914 as an active pharmaceutical ingredient.

17. When a crystalline material is provided in higher purity, it has a higher melting point. When a crystalline material is provided in lighter color, it has a higher purity. Thus, with respect to the subject matter of Claims 24-26, it is clear that the higher melting point (relative to the lower melting point reported by Kim) and white color (relative to the yellow color reported by Kim) are indicative of higher purity.

18. Those of skill in the art interested in obtaining material with higher purity would have a variety of possible ways to modify the process taught by Kim et al. These possible ways include: such as changing the solvent in the first dissolution-evaporation step in Kim et al., changing the solvent in the second dissolution-evaporation step or in the recrystallization stage, or replacing any of the three above-mentioned steps in Kim et al. by a different purification technique, such as extraction, sublimation, crystallization or chromatography. Indeed, Cook (cited in the Office Action in combination with Kim) teaches using different recrystallization solvents, and using chromatography, which are examples of these possible different approaches.

19. Rather than leading one to use isopropanol to increase the purity, Kim discloses on page 15, lines 19-23, that:

"the compound of formula I can be purified by crystallization from ether in high yield and high purity (m.p.: 183-185°C)".

Therefore, Kim does not teach or suggest that the use of isopropanol could have any effect on the final purity of VA-2914.

20. We have surprisingly found that VA-2914 isopropanol hemisolvate presents very special solubility properties (lower solubility) that make it a highly useful intermediate in the process of purification of VA-2914 when obtained by recrystallization. As a consequence, the process as claimed affords VA-2914 with an improved purity. However, if this hemisolvate is not prepared by recrystallization, the process does not benefit from the unexpected solubility properties of the hemisolvate. That is, the increased purity is a result of separating the compound from the mother liquor, because the mother liquor includes various soluble impurities that otherwise would be retained.

21. It is also relevant to note that Kim et al. published a paper (Steroids 2000, 65, 395-400), copy enclosed, where the results of their previous patent were described (see page 396, first paragraph, last sentence - reference [9] refers to the U.S. patent application whose

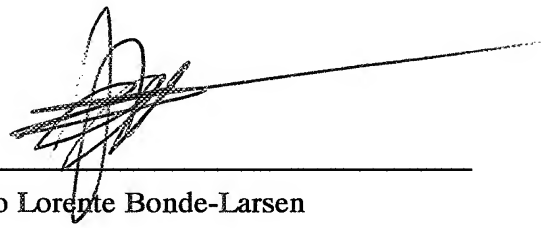
priority is claimed by Kim et al.). In this paper, the synthesis and purification of VA-2914 (compound 8 of the publication) is described in point 2.7. In this case, the dissolution-evaporation stage of the raw material in isopropanol was removed and so the product was just purified by a dissolution-evaporation stage in ethyl acetate followed by recrystallization. However, a product with a similar melting point as in Kim et al. was obtained (m.p. = 183-185°C), thus indicating that the dissolution-evaporation step in isopropanol did not influence the purity of the final compound. This is in stark contrast to the instantly claimed process, in which the recrystallization step from isopropanol allows one to improve the purity of the final product.

22. It is also relevant that when purifying raw VA-2914, the inventors evaluated several crystallization solvents, including ethyl acetate, ethyl alcohol, isopropyl ether, and acetone/water. However, in all cases, yellow crystals of VA-2914 with relatively low purity were obtained. Subsequent recrystallizations from the same or different solvents did not allow them to improve the purity. Surprisingly, only the use of isopropanol as a first recrystallization solvent gave rise to the formation of a hemisolvate derivative with unexpected solubility properties, which allowed the development of a new process of purification of VA-2914 which afforded the desired compound in higher purity.

23. In other words, the problem solved by the present invention is not achieved by the mere use of an additional recrystallization step in the purification process, but by the use of isopropanol in a first recrystallization, which confers advantageous solubility properties to the resulting product (i.e., the hemisolvate is insoluble in the solvent, whereas the various (colored) impurities remain in the mother liquor). As already discussed, the skilled person would not infer from Kim that the isopropanol hemisolvate could have any advantageous solubility properties, and would therefore not find any guidance on how to arrive at an improved purification process for VA-2914.

24. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like

so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 03/MAR 5/2010 By: 

Antonio Lorente Bonde-Larsen

Raw VA-2914 (purity = 87.50%)

Project Name: EXD_ULR_2010_01
User Name: HO Plaga (Laboratorio)
Software Empower 2 Software Suit

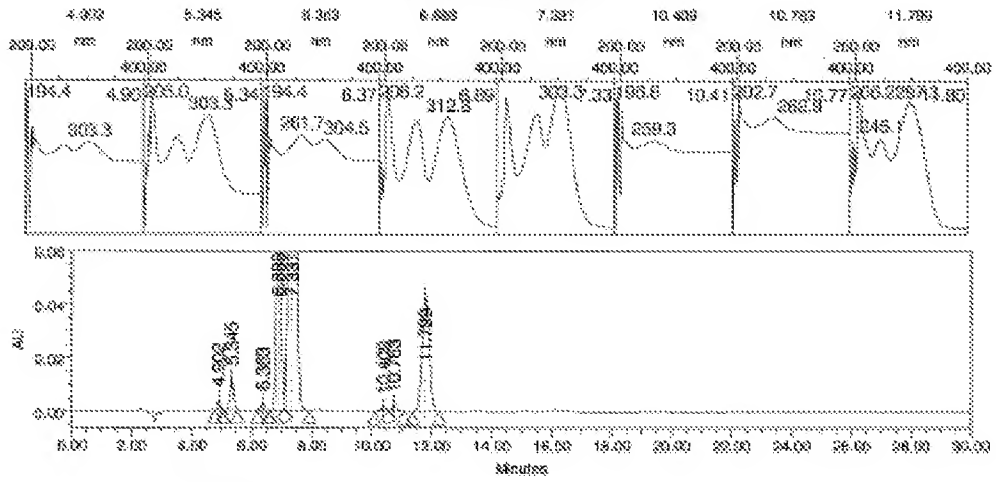
Report Method Name pureza ampliado 036
Current Date: 15/01/2010

RAGACTIVES Sample Information

SampleName: ULR_OMM_024_FO
Vial: 60
Injection: 1
Injection Volume: 10.00 ul
Mobile_phase KH2PO4(pH=7)/ACN/THF
Solvents_used SOL470/V0091/V0038
Flow: 1.0
Wavelength: PDA
Column_batch CC383

Date Acquired: 14/01/2010 2:01:04 PM CET
Acq Method Set: U0604
Processing Method: purity
Date Processed: 14/01/2010 4:39:38 PM CET
Run Time: 30.0 Minutes
Processed Channel Descr.: PDA 254.0 nm
Column_type X-terra_C18_250mm
System Name HPLC 16

Spectrum Index Plot



Peak Results

	Name	RT	Area	% Area	Purity 1 Angle	Purity 1 Threshold
1		4.902	28024	0.20	0.358	0.551
2		5.345	104408	0.73	1.181	0.357
3		6.363	24302	0.17	1.127	0.884
4		6.888	847458	5.92	0.302	0.218
5		7.331	12626808	87.50	0.110	0.376
6		10.409	23838	0.17	1.391	1.821
7		10.783	37090	0.26	1.227	1.282

	Name	RT	Area	% Area	Purity 1 Angle	Purity 1 Threshold
8		11.799	728558	5.05	0.082	0.322

VA-2914 purified by the process of Kim et al. (purity = 98.57%)

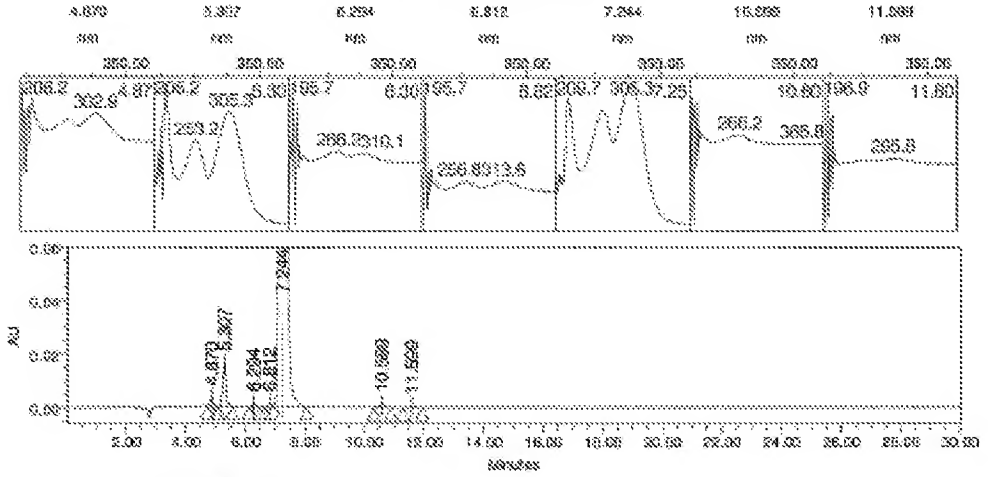
Project Name: [illegible]
User Name: [illegible]
Software Empower 2 Software Build
Report Method Name: [illegible]
Current Date: 18/01/2010

RAGACTIVES Sample Information

SampleName: [illegible]
Vial: 61
Injection: 1
Injection Volume: 10.00 ul
Mobile_phase: [illegible]
Solvents_used: [illegible]
Flow: 1.0
Wavelength: PDA
Column_batch: [illegible]

Date Acquired: 18/01/2010 17:27:10 CET
Acq Method Set: [illegible]
Processing Method: purity
Date Processed: 18/01/2010 19:03:54 CET
Run Time: 30.0 Minutes
Processed Channel Descr.: PDA 254.0 nm
Column_type: XBridge C18 250mm
System Name: QL14

Spectrum Index Plot



Peak Results

	Name	RT	Area	% Area	Purity1 Angle	Purity1 Threshold
1		4.870	21838	0.18	1.570	1.104
2		5.307	109004	0.87	0.317	0.384
3		6.254	8593	0.06	4.596	3.304
4		6.812	11262	0.08	2.353	2.392
5		7.244	13470147	98.57	0.111	0.470
6		10.886	14648	0.11	4.982	3.715
7		11.560	5661	0.04	10.106	6.259

VA-2914 purified by the process of the invention (purity = 99.20%)

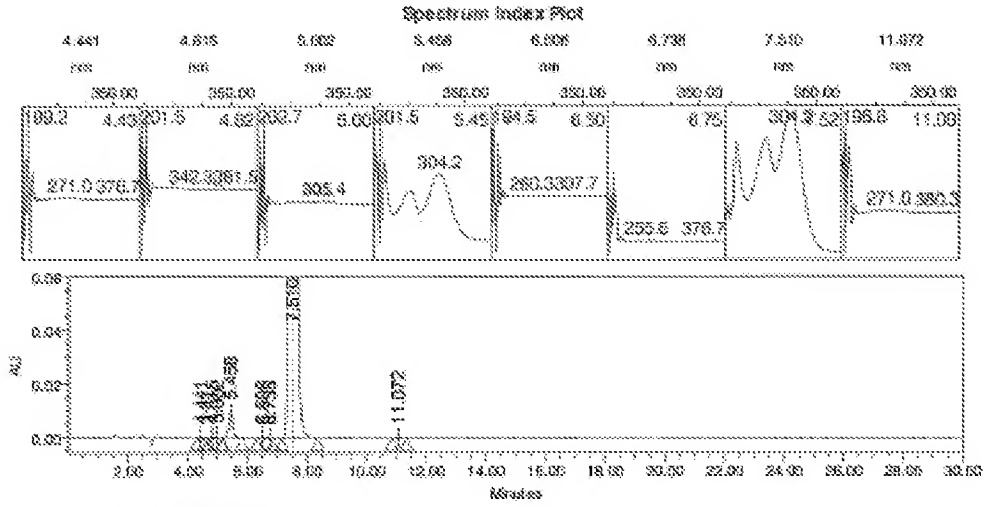
Project Name IDID_ULE_2010_01
User Name I+D Reps (Laboratorio)
Software Empower 2 Software Build

Report Method Name pureza amplada 008
Current Date 18/01/2010

RAGACTIVES Sample Information

SampleName ULE_CM4_025_TS-02
Vial 31
Injection 1
Injection Volume 10.00 ul
Mobile_phase K+PO4(pH=7)/ACN/THF
Solvents_used SOL470/V0091/V0038
Flow 1.0
Wavelength PDA
Column_batch CC383

Date Acquired 18/01/2010 2:37:46 PM CET
Acq Method Set UD604_W2996
Processing Method purity
Date Processed 18/01/2010 3:40:04 PM CET
Run Time 30.0 Minutes
Processed Channel Descr. PDA 254.0 nm
Column_type XBridge C18 250mm
System Name HPLC07



Peak Results

	Name	RT	Area	% Area	Purity 1 Angle	Purity 1 Threshold
1		4.441	1254	0.01	13.243	22.808
2		4.815	1867	0.01		
3		5.002	4039	0.03	5.167	6.859
4		5.488	88283	0.69	3.350	6.720
5		6.008	2377	0.02	19.382	19.654
6		6.738	1026	0.01	25.216	27.798
7		7.519	12839612	99.20	0.054	0.395

	Name	RT	Area	% Area	Purity 1 Angle	Purity 1 Threshold
8		11.072	3861	0.03	13.702	17.519

ANNEX 2

Ragactives	**CURRICULUM VITAE**

ANTONIO LORENTE BONDE-LARSEN
Research & Development
CRYSTAL PHARMA, S.A.
e-mail: antonio.lorente@gadea.com

EDUCATIONAL BACKGROUND

- B.S. in Chemistry (Organic Chemistry). Universidad Autónoma de Madrid, Spain.
- Ph.D. in Chemistry (Organic Chemistry). Universidad Autónoma de Madrid, Spain.

TRAINING

- *Training on patents and utility models: data, patentability, drafting, transference, infraction and court actions*. Centre de Patentes de la Universitat de Barcelona and Oficina Española de Patentes y Marcas.
- *Information, search of patents and international regulations*. Oficina Española de Patentes y Marcas.
- *STN Information search*, directed to the search of patents and products of pharmaceutical interest. Centre d´Estudis de Documentació de Patents.

PUBLICATIONS

- *"Chemoselective hydrogenation of 17-alpha-hydroxy-6-mehtylen-pregna-4,9(11)-diene-3,20-dione. Synthesis of Fluorometholone"*, Tetrahedron 2009, Vol. 65(41), pp. 8493-8496.
- *"1,2-dehydrogenation of steroidal 6-methylen derivatives. Synthesis of Exemestane"*, Tetrahedron 2009, Vol. 65(36), pp. 7587-7590.

- *" Highly stereoselective reduction of acyclic α-sulfinildetimines: Synthesis of enantioamerically pure β-aminosulfoxides"*, Tetrahedron Asymmetry 1999, Vol. 10(23), pp. 4607-4618.
- "*Enantiomerically pure 2-alkyl-and 2,3-dialkylaziridines from 2-sulfinylimines"*, Tetrahedron Letters 1998, Vol. 39(52), pp. 9765-9768.
- "*Synthesis of enantiomerically pure acyclic α-sulfinilketimines"*, Tetrahedron Asymmetry 1998, Vol. 9(14), pp. 2437-2450.
- *"Asymmetric Diels Alder Reactions of γ-Alkoxy-α-sulfinilbutenolides"*, Tetrahedron Asymmetry 1993, Vol. 4(2), pp.177-180.
- *"Synthesis and stereoselective reductions of Chiral-iminosulfóxides"*, Tetrahedron Letters, 1992, Vol. 33(38), pp. 5637-5640.

PATENTS

- "Procedimiento para la obtención de 17β-(N-terc-butilcarbamoil)-3-ona-4-aza esteroides", WO 2001/002422 - ES 2153789 B1 - EP 1116725 B1 - US 6,509,466.
- "Procedimiento para la obtención de 17β-(sustituido) –3-oxo-$\Delta^{1,2}$-4-azaesteroides", WO 2003/0292 67 A2 – ES 2185503 A1 – EP 1437361 A2.
- "Procedimiento para la obtención de 4-alquilamino-5,6-dihidro-4H-tieno-(2,3b)-tiopirán-2-sulfonamida-7-dióxidos e intermedios", WO 02/20529 – EP 1329453 B1 – ES 2177415.
- "Procedimiento para la separación de R(-)- y S(+)-5-[2-[[2-(2-etoxifenoxi)etil]amino]propil-2-metoxibencenosulfonamida", WO 2004/006829 – ES 2200699 A1.
- "Procedimiento e intermedios para la obtención de derivados de 1-(1H-bencimicazol-2-il)-4-(2-aminopirimidin)piperidina", WO 2004/031170 – ES 2208098 A1.
- "Procedimiento para la síntesis de Pantoprazol e intermedios", ES 2201936.
- "Crystalline forms of mizolastine, production methods thereof and pharmaceutical compositions containing same", WO 2005/096692.
- "Procedimiento para la obtención de 3,3-difenilpropilaminas", ES P 2005 01990.